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Remington's

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Pharmaceutical Sciences

1990

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Remington's Pharmaceutical Sciences . . . *a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . A textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences.*

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Ampholytes

Substances such as $NaHCO_3$ and NaH_2PO_4 are termed *ampholytes*, and are capable of functioning both as acids and bases. When an ampholyte of the type NaHA is dissolved in water, the following series of reactions can occur

$$Na^+HA^- \xrightarrow{H_2O} Na^+ + HA^-$$

$$HA^- + H_2O \rightleftharpoons A^{2-} + H_3O^+$$

$$HA^- + H_2O \rightleftharpoons H_2A + OH^-$$

$$2H_2O \rightleftharpoons H_3O^+ + OH^-$$

The total proton balance equation (PBE) for the system is

$$[H_3O^+] + [H_2A] = [OH^-] + [A^{2-}] \qquad (72)$$

Substituting both $[H_2A]$ and $[A^{2-}]$ as a function of $[H_3O^+]$ (see Eqs 52 and 54), yields

$$[H_3O^+] + \frac{[H_3O^+]^2 C_s}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} =$$

$$\frac{K_w}{[H_3O^+]} + \frac{K_1K_2C_s}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2}$$

This gives a fourth-order equation in $[H_3O^+]$, which can be simplified using certain judicious assumptions to

$$[H_3O^+] = \sqrt{\frac{K_1K_2C_s}{K_1 + C_s}} \qquad (73)$$

In most instances, $C_s \gg K_1$ and the equation further simplifies to

$$[H_3O^+] = \sqrt{K_1K_2} \qquad (74)$$

and $[H_3O^+]$ becomes independent of the concentration of the salt. A special property of ampholytes is that the concentration of the species HA^- is maximum at the pH corresponding to Eq 74.

When the simplest amino acid salt, glycine hydrochloride, is dissolved in water, it acts as a diprotic acid and ionizes as

$$^+NH_3CH_2COOH + H_2O \rightleftharpoons {}^+NH_3CH_2COO^- + H_3O^+$$

$$^+NH_3CH_2COO^- + H_2O \rightleftharpoons NH_2CH_2COO^- + H_3O^+$$

The form, $^+NH_3CH_2COO^-$, is an ampholyte since it also can act as a weak base

$$^+NH_3CH_2COO^- + H_2O \rightleftharpoons {}^+NH_3CH_2COOH + OH^-$$

This type of substance, which carries both a charged acidic and a charged basic moiety on the same molecule is termed a *zwitterion* and, since the two charges balance each other, the molecule acts essentially as a neutral molecule. The pH at which the *zwitterion* concentration is maximum is known as the isoelectric point, which can be calculated from Eq 74.

On the acid side of the isoelectric point, amino acids and proteins are cationic and incompatible with anionic materials such as the naturally occurring gums used as suspending and/or emulsifying agents. On the alkaline side of the isoelectric point, amino acids and proteins are anionic and incompatible with cationic materials such as benzalkonium chloride.

Salts of Weak Acids and Weak Bases

When a salt such as ammonium acetate (which is derived from a weak acid and a weak base) is dissolved in water, it undergoes the following reactions

$$BH^+A^- \xrightarrow{H_2O} BH^+ + A^-$$

$$BH^+ + H_2O \rightleftharpoons B + H_3O^+$$

$$A^- + H_2O \rightleftharpoons HA + OH^-$$

The total PBE for this system is

$$[H_3O^+] + [HA] = [OH^-] + [B] \qquad (75)$$

Replacing [HA] and [B] as a function of $[H_3O^+]$, gives

$$[H_3O^+] + \frac{[H_3O^+]C_s}{[H_3O^+] + K_a} = [OH^-] + \frac{K_a'C_s}{[H_3O^+] + K_a'} \qquad (76)$$

in which C_s is the concentration of salt, K_a is the ionization constant of the conjugate acid formed from the reaction between A^- and water and K_a' is the ionization constant for the protonated base, BH^+. In general, $[H_3O^+]$, $[OH^-]$, K_a and K_a' usually are smaller than C_s and the equation simplifies to

$$[H_3O^+] = \sqrt{K_aK_a'} \qquad (77)$$

Example—Calculate the pH of a 0.01 *M* solution of ammonium acetate. The ammonium ion has a K_a equal to 5.75×10^{-10}, which represents K_a' in Eq 77. Acetic acid has a K_a of 1.75×10^{-5}, which represents K_a in Eq 77

$$[H_3O^+] = \sqrt{1.75 \times 10^{-5} \times 5.75 \times 10^{-10}}$$

$$= 1.05 \times 10^{-7}$$

$$pH = -\log (1.05 \times 10^{-7}) = 6.98$$

All of the assumptions are valid.

Buffers

The terms *buffer*, *buffer solution* and *buffered solution*, when used with reference to hydrogen-ion concentration or pH, refer to the ability of a system, particularly an aqueous solution, to resist a change of pH on adding acid or alkali, or on dilution with a solvent.

If an acid or base is added to water, the pH of the latter is changed markedly, for water has no ability to resist change of pH; it is completely devoid of buffer action. Even a very weak acid such as carbon dioxide changes the pH of water, decreasing it from 7 to 5.7 when the small concentration of carbon dioxide present in air is equilibrated with pure water. This extreme susceptibility of distilled water to a change of pH on adding very small amounts of acid or base is often of great concern in pharmaceutical operations. Solutions of neutral salts, such as sodium chloride, similarly lack ability to resist change of pH on adding acid or base; such solutions are called unbuffered.

Characteristic of buffered solutions, which undergo small changes of pH on addition of acid or base, is the presence either of a weak acid and a salt of the weak acid, or a weak base and a salt of the weak base. An example of the former system is acetic acid and sodium acetate; of the latter, ammonium hydroxide and ammonium chloride. From the proton concept of acids and bases discussed earlier, it is apparent that such buffer action involves a conjugate acid–base pair in the solution. It will be recalled that acetate ion is the conjugate base of acetic acid, and that ammonium ion is the conjugate acid of ammonia (the principal constituent of what commonly is called ammonium hydroxide).

The mechanism of action of the acetic acid–sodium acetate buffer pair is that the acid, which exists largely in molecular (nonionized) form, combines with hydroxyl ion that may be added to form acetate ion and water, thus

$$CH_3COOH + OH^- \rightarrow CH_3COO^- + H_2O$$

while the acetate ion, which is a base, combines with hydrogen (more exactly hydronium) ion that may be added to

form essentially nonionized acetic acid and water, represented as

$$CH_3COO^- + H_3O^+ \rightarrow CH_3COOH + H_2O$$

As will be illustrated later by an example, the change of pH is slight as long as the amount of hydronium or hydroxyl ion added does not exceed the capacity of the buffer system to neutralize it.

The ammonia–ammonium chloride pair functions as a buffer because the ammonia combines with hydronium ion that may be added to form ammonium ion and water, thus

$$NH_3 + H_3O^+ \rightarrow NH_4^+ + H_2O$$

Ammonium ion, which is an acid, combines with added hydroxyl ion to form ammonia and water, as

$$NH_4^+ + OH^- \rightarrow NH_3 + H_2O$$

Again, the change of pH is slight if the amount of added hydronium or hydroxyl ion is not in excess of the capacity of the system to neutralize it.

Besides these two general types of buffers, a third appears to exist. This is the buffer system composed of two salts, as monobasic potassium phosphate, KH_2PO_4, and dibasic potassium phosphate, K_2HPO_4. This is not, however, a new type of buffer; it is actually a weak-acid–conjugate-base buffer in which an ion, $H_2PO_4^-$, serves as the weak acid, and HPO_4^{2-} is its conjugate base. When hydroxyl ion is added to this buffer the following reaction takes place

$$H_2PO_4^- + OH^- \rightarrow HPO_4^{2-} + H_2O$$

and when hydronium ion is added

$$HPO_4^{2-} + H_3O^+ \rightarrow H_2PO_4^- + H_2O$$

It is apparent that the mechanism of action of this type of buffer is essentially the same as that of the weak-acid–conjugate-base buffer composed of acetic acid and sodium acetate.

Calculations—A buffer system composed of a conjugate acid–base pair, NaA – HA (such as sodium acetate and acetic acid), would have a PBE of

$$[H_3O^+] + [HA] = [OH^-] + [A^-] \qquad (78)$$

Replacing [HA] and $[A^-]$ as a function of hydronium-ion concentration gives

$$[H_3O^+] + \frac{[H_3O^+]C_b}{[H_3O^+] + K_a} = [OH^-] + \frac{K_aC_a}{[H_3O^+] + K_a} \qquad (79)$$

where C_b is the concentration of the salt, NaA, and C_a is the concentration of the weak acid, HA. This equation can be rearranged to give

$$[H_3O^+] = K_a \frac{(C_a - [H_3O^+] + [OH^-])}{(C_b + [H_3O^+] - [OH^-])} \qquad (80)$$

In general, both C_a and C_b are much greater than $[H_3O^+]$, which is in turn much greater than $[OH^-]$, and the equation simplifies to

$$[H_3O^+] = \frac{K_aC_a}{C_b} \qquad (81)$$

or, expressed in terms of pH, as

$$pH = pK_a + \log \frac{C_b}{C_a} \qquad (82)$$

This equation is generally called the Henderson–Hasselbalch equation. It applies to all buffer systems formed from a single conjugate acid–base pair, regardless of the nature of the salts. For example, it applies equally well to the following buffer systems: ammonia–ammonium chloride, monosodium phosphate–disodium phosphate, phenobarbital–sodium phenobarbital, etc. In the ammonia–ammonium chloride system, ammonia is obviously the base and the ammonium ion is the acid (C_a equal to the concentration of the salt). In the phosphate system, monosodium phosphate is the acid and disodium phosphate is the base. For the phenobarbital buffer system, phenobarbital is the acid and the phenobarbital anion is the base (C_b equal to the concentration of sodium phenobarbital).

As an example of the application of this equation, the pH of a buffer solution containing acetic acid and sodium acetate, each in 0.1 *M* concentration, may be calculated. The K_a of acetic acid, as defined above, is 1.8×10^{-5}, at 25°.

Solution

First, the pK_a of acetic acid is calculated

$$pK_a = -\log K_a = -\log 1.8 \times 10^{-5}$$
$$= -\log 1.8 - \log 10^{-5}$$
$$= -0.26 - (-5) = +4.74$$

Substituting this value into Eq 82

$$pH = \log \frac{0.1}{0.1} + 4.74 = +4.74$$

The Henderson–Hasselbalch equation predicts that any solutions containing the same molar concentration of acetic acid as of sodium acetate will have the same pH. Thus, a solution of 0.01 *M* concentration of each will have the same pH, 4.74, as one of 0.1 *M* concentration of each component. Actually, there will be some difference in the pH of the solutions, for the *activity coefficient* of the components varies with concentration. For most practical purposes, however, the approximate values of pH calculated by the equation are satisfactory. It should be pointed out, however, that the buffer of higher concentration of each component will have a much greater capacity for neutralizing added acid or base and this point will be discussed further under *Buffer Capacity*.

The Henderson–Hasselbalch equation is useful also for calculating the ratio of molar concentrations of a buffer system required to produce a solution of specific pH. As an example, suppose that an acetic acid–sodium acetate buffer of pH 4.5 is to be prepared. What ratio of the buffer components should be used?

Solution

Rearranging Eq 82, which is used to calculate the pH of weak acid-salt type buffers, gives

$$\log \frac{[\text{base}]}{[\text{acid}]} = pH - pK_a$$
$$= 4.5 - 4.76 = -0.24 = (9.76 - 10)$$
$$\frac{[\text{base}]}{[\text{acid}]} = \text{antilog of } (9.76 - 10) = 0.575$$

The interpretation of this result is that the *proportion* of sodium acetate to acetic acid should be 0.575 mole of the former to 1 mole of the latter to produce a pH of 4.5. A solution containing 0.0575 mole of sodium acetate and 0.1 mole of acetic acid per liter would meet this requirement, as would also one containing 0.00575 mole of sodium acetate and 0.01 mole of acetic acid per liter. The actual concentration selected would depend chiefly on the desired buffer capacity.

Buffer Capacity—The ability of a buffer solution to resist changes in pH upon addition of acid or alkali may be measured in terms of *buffer capacity*. In the preceding discussion of buffers, it has been seen that, in a general way, the concentration of acid in a weak-acid–conjugate-base buffer determines the capacity to "neutralize" added base,

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while the concentration of salt of the weak acid determines the capacity to neutralize added acid. Similarly, in a weak-base–conjugate-acid buffer the concentration of the weak base establishes the buffer capacity toward added acid, while the concentration of the conjugate acid of the weak base determines the capacity toward added base. When the buffer is equimolar in the concentrations of weak acid and conjugate base, or of weak base and conjugate acid, it has equal buffer capacity toward added strong acid or strong base.

Van Slyke, the biochemist, introduced a quantitative expression for evaluating buffer capacity. This may be defined as the amount, in gram-equivalents (g-Eq) per liter, of strong acid or strong base, required to be added to a solution to change its pH by 1 unit; a solution has a buffer capacity of 1 when 1 L requires 1 g-Eq of strong base or acid to change the pH 1 unit (in practice, considerably smaller increments are measured, expressed as the ratio of acid or base added to the change of pH produced). From this definition it is apparent that the smaller the pH change in a solution caused by the addition of a specified quantity of acid or alkali, the greater the buffer capacity of the solution.

The following numerical examples illustrate certain basic principles and calculations concerning buffer action and buffer capacity.

Example 1—What is the change of pH on adding 0.01 mole of NaOH to 1 L of 0.10 *M* acetic acid?

(a) Calculate the pH of a 0.10 molar solution of acetic acid

$$[H_3O^+] = \sqrt{K_a C_a} = \sqrt{1.75 \times 10^{-4} \times 1.0 \times 10^{-1}} = 1.33 \times 10^{-3}$$

$$pH = -\log 1.33 \times 10^{-3} = 2.88$$

(b) On adding 0.01 mole of NaOH to a liter of this solution, 0.01 mole of acetic acid is converted to 0.01 mole of sodium acetate, thereby decreasing C_a to 0.09 *M*, and $C_b = 1.0 \times 10^{-2}$ *M*. Using the Henderson–Hasselbach equation gives

$$pH = 4.76 + \log \frac{0.01}{0.09} = 4.76 - 0.95 = 3.81$$

The pH change is, therefore, 0.93 unit. The buffer capacity as defined above is calculated to be

$$\frac{\text{moles of NaOH added}}{\text{change in pH}} = 0.011$$

Example 2—What is the change of pH on adding 0.1 mole of NaOH to 1 L of buffer solution 0.1 *M* in acetic acid and 0.1 *M* in sodium acetate?

(a) The pH of the buffer solution before adding NaOH is

$$pH = \log \frac{[\text{base}]}{[\text{acid}]} + pK_a$$

$$= \log \frac{0.1}{0.1} + 4.76 = 4.76$$

(b) On adding 0.01 mole of NaOH per liter to this buffer solution, 0.01 mole of acetic acid is converted to 0.01 mole of sodium acetate, thereby decreasing the concentration of acid to 0.09 *M* and increasing the concentration of base to 0.11 *M*. The pH is calculated as

$$pH = \log \frac{0.11}{0.09} + 4.76$$

$$= 0.086 + 4.76 = 4.85$$

The change of pH in this case is only 0.09 unit, about 1/10 the change in the preceding example. The buffer capacity is calculated as

$$\frac{\text{moles of NaOH added}}{\text{change of pH}} = \frac{0.01}{0.09} = 0.11$$

Thus, the buffer capacity of the acetic acid–sodium acetate buffer solution is approximately 10 times that of the acetic acid solution.

As is in part evident from these examples, and may be further evidenced by calculations of pH changes in other systems, the degree of buffer action and, therefore, the buffer capacity, depend on the kind and concentration of the buffer components, the pH region involved and the kind of acid or alkali added.

Strong Acids and Bases as "Buffers"—In the foregoing discussion, buffer action was attributed to systems of (1) weak acids and their conjugate bases, (2) weak bases and their conjugate acids and (3) certain acid-base pairs which can function in the manner either of System 1 or 2.

The ability to resist change in pH on adding acid or alkali is possessed also by relatively concentrated solutions of strong acids and strong bases. If to 1 L of pure water having a pH of 7.0 is added 1 mL of 0.01 *M* hydrochloric acid, the pH is reduced to about 5.0. If the same volume of the acid is added to 1 L of 0.001 *M* hydrochloric acid, which has a pH of about 3, the hydronium-ion concentration is increased only about 1% and the pH is reduced hardly at all. The nature of this buffer action is quite different from that of the true buffer solutions. The very simple explanation is that when 1 mL of 0.01 *M* HCl, which represents 0.00001 g-Eq of hydronium ions, is added to the 0.0000001 g-Eq of hydronium ions in 1 L of pure water, the hydronium-ion concentration is increased 100-fold (equivalent to 2 pH units), but when the same amount is added to the 0.001 g-Eq of hydronium ions in 1 L of 0.001 *M* HCl, the increase is only 1/100 the concentration already present. Similarly, if 1 mL of 0.01 *M* NaOH is added to 1 L of pure water, the pH is increased to 9, while if the same volume is added to 1 L of 0.001 molar NaOH, the pH is increased almost immeasurably.

In general, solutions of strong acids of pH 3 or less, and solutions of strong bases of pH 11 or more, exhibit this kind of buffer action by virtue of the relatively high concentration of hydronium or hydroxyl ions present. The USP includes among its *Standard Buffer Solutions* a series of hydrochloric acid buffers, covering the pH range 1.2 to 2.2, which also contain potassium chloride. The salt does not participate in the buffering mechanism, as is the case with salts of weak acids; instead, it serves as a nonreactive constituent required to maintain the proper electrolyte environment of the solutions.

Determination of pH

Colorimetry

A relatively simple and inexpensive method for determining the approximate pH of a solution depends on the fact that some conjugate acid base pairs (indicators) possess one color in the acid form and another color in the base form. Assume that the acid form of a particular indicator is red, while the base form is yellow. The color of a solution of this indicator will range from red, when it is sufficiently acid, to yellow, when it is sufficiently alkaline. In the intermediate pH range (the transition interval) the color will be a blend of red and yellow depending upon the ratio of the base to the acid form. In general, although there are slight differences between indicators, color changes apparent to the eye cannot be discerned when the ratio of base to acid form, or acid to base form exceeds 10:1. The use of Eq 82 indicates that the transition range of most indicators is equal to the pK_a of the indicator ±1 pH unit, or a useful range of approximately 2 pH units. Standard indicator solutions can be made at known pH values within the transition range of the indicator, and the pH of an unknown solution determined by adding the indicator to it and comparing the resulting color with the standard solutions. Details of this procedure can be found in RPS-14. Another method for using these indicators is to apply them to thin strips of filter paper. A drop of the unknown solution is placed on a piece of the indicator paper and the resulting color compared to a color chart supplied with the indicator paper. These papers are available in a wide variety of pH ranges.

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